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(71) Applicant *(for all designated States except US)*: BUKH MEDITEC A/S [DK/DK]; Strandvejen 122, DK-2900 Hellerup (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BAR-SHALOM, Daniel [IL/DK]; Rypervænget 213, DK-2980 Kokkedal (DK). BUKH, Niels [DK/DK]; Strandvejen 122, DK-2900 Hellerup (DK).

(74) Agent: PLOUGMANN & VINGTOFT; Sankt Annæ Plads 11, DK-1250 Copenhagen K (DK).

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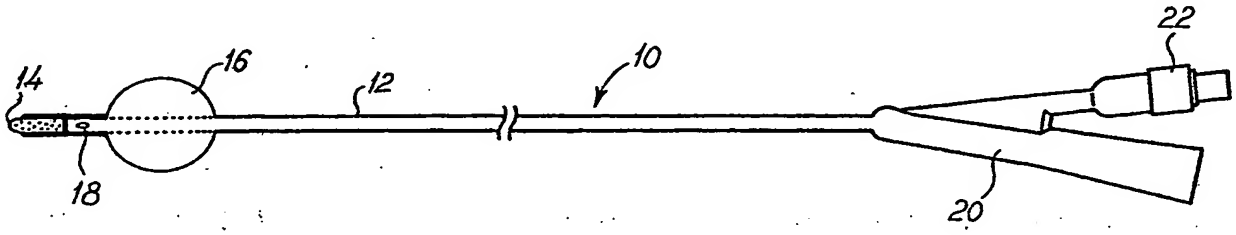

(57) Abstract

A medical device intended for introduction into a body cavity, the device comprising, at one end thereof adapted to be inserted into said body cavity, a matrix in which an active substance is embedded and from which it is released at a predetermined rate, the matrix being composed of a substance which is not or only slightly penetrable to water, the device further preferably comprising a tube and/or rod for the drainage and/or delivery of fluids into said body cavity. The active substance may be selected from antimicrobial agents, anesthetics, analgesics, antiinflammatory agents, antiseptic agents, growth factors, hormones, disinfectants, counterirritants, coagulation modifying agents, wound-healing promoters, antiviral agents and antineoplastic or cytostatic agents or other agents with anticancer properties, or a combination thereof. The device permits substantially direct delivery of an active substance to or close to the site where it will exert its activity, e.g. via a catheter, and is able to prevent or reduce the incidence of infections arising from the use of medical devices which are inserted into a body cavity.

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A MEDICAL DEVICE FOR INTRODUCTION INTO A BODY CAVITY

FIELD OF INVENTION

The present invention relates to a medical device intended for introduction into a body cavity, the device comprising a therapeutically active substance which is gradually released from the device.

BACKGROUND OF THE INVENTION

The clinical use of medical devices which comprise a part, usually a tube, rod, cannula or the like, typically made of metal or a plastic material and intended for insertion into a body cavity, and which are intended to reside in the body for a certain period of time, often gives rise to complications such as infections or thrombophlebitis. It has been shown, for instance, (O.B. Jepsen, "Prevention of Procedure Related Nosocomial Infections", *Proceedings. 13th Int. Congress of Chemotherapy*, Vienna 1983, Sy 52/6, pp. 6/29-6/36) that the occurrence of urinary tract infection is connected with the use of urethral catheters. Similarly, the development of thrombophlebitis, local infection and bacteremia is associated with the use of venous catheters (O.B. Jepsen, *op. cit.*). Similar effects have also been observed with the use of respiratory aids, devices used for endoscopic examination, ostomy appliances and drainage tubes.

The exact mechanisms governing the development of such infections have not yet been fully understood. In recent years, however, the observation of bacterial colonization of the surfaces of invasive devices has attracted increasing attention. The bacterial colonies are often enclosed by the so-called bacterial glycocalyx; this term is understood to mean any polysaccharide-containing component found outside the bacterial cell wall. The glycocalyx is usually composed of fibrous polysaccharides and/or globular glycoproteins, and these molecules are essentially the sole components found on the surface of wild-type bacterial strains capable of growing and surviving in competitive environments. The bacterial glycocalyx serves an important

function for the adhesion of bacteria to each other as well as to inert surfaces to form adherent colonies which are the predominant form of bacterial growth.

It has been demonstrated (J.W. Costerton, "The Bacterial Glycocalyx in Nature and Disease", *Am. Rev. Microbiol. 35*, 1981, pp. 299-324) that the glycocalyx begins to form immediately after the insertion of a medical device into a body cavity, as many of the plastic materials of which such devices are usually composed have the ability to attract bacteria and encourage colonization. The bacteria may then migrate along the catheter tract subcutaneously or inside the lumen and eventually give rise to infection in the vicinity of the inserted device. Thus, for instance, coagulase-negative staphylococci appear to be infrequent pathogens unless they adhere to foreign bodies such as medical devices introduced into a body cavity, but coagulase-negative staphylococci have become increasingly recognized to be important pathogens in the presence of devices such as intravascular grafts, prosthetic heart valves, vascular catheters and orthopaedic and neurosurgical implants. The organism gains access to the device at the time of surgery or catheter placement and forms colonies, although infection may not become clinically evident until several days or even several months after the initial contamination event.

It has furthermore been shown (T.R. Franson et al., "Persistent in-Vitro Survival of Coagulase-Negative Staphylococci Adherent to Intravascular Catheters in the Absence of Conventional Nutrients", *J. Clin. Microbiol. 24*(4), 1986, pp. 559-564) that coagulase-negative staphylococci, and presumably other bacteria as well, are able to survive *in vitro* in media devoid of conventional nutrients in the presence of plastic catheter materials (in particular polyvinylchloride) and tend to proliferate on catheters in the presence of nutrients.

It is estimated that the risk for patients provided with a urethral catheter (about 10% of all hospitalized patients) of developing a urinary tract infection is about 10 times that of non-catheterized patients, while their risk of developing bacteremia is about 3 times

higher. Similarly, about 25-50% of all hospitalized patients are provided with an intravenous catheter, and for these patients the risk of developing an infection resulting from the use of a catheter is about 7 times that of non-catheterized patients. In case of central venous catheters, the risk of developing an infection due to the presence of the catheter increases about 90 fold.

Numerous solutions to the problem of infections resulting from the use of urethral catheters in particular have been proposed (cf. US 4,601,880, US 4,571,241, WO 86/00816, US 4,534,768, EP 150666, JP 60 80458, JP 60 80457, JP 60 40061, JP 59 228856, US 4,505,703, US 4,464,258, US 4,475,910, US 4,642,104, EP 65884, US 4,479,795, DE 2450804). For instance, it has been suggested to provide an antimicrobial agent in a polymeric coating on the catheter or incorporated in the catheter wall material itself. The antimicrobial agent then diffuses from the coating or the catheter wall when the catheter is inserted in the body cavity. It is problematic, however, to rely on diffusion of a drug from the coating or catheter wall: firstly, the drug may be unstable in an aqueous environment. As it is brought into contact with water (as present in biological fluids, e.g. urine) diffusing into the coating or wall material before it is released, its stability may therefore be compromised before it has had the opportunity to exert its activity. In other words, a substantial proportion of drug may have become inactive before release so that little or no beneficial effect of its presence in the device can be detected. Secondly, it is very difficult to obtain a reliable, constant release rate of the drug over a longer period of time when the drug is released by diffusion.

Another approach which is currently being used in some countries is to irrigate the bladder continuously with an antibiotic solution by means of a special three-way catheter. This regimen, however, necessitates immobilization of the patient, for which reason it has limited practical utility.

Thus, there is a need to develop catheters and similar medical devices which may be used to reduce the risk of infections ascribable to the use of conventional devices of this type, and from which an

active substance is reproducibly available through slow release for as long as the device is present in the body cavity into which it is inserted.

Apart from this, it would also be an advantage to provide a medical device through which an active substance other than an antibiotic may be administered locally. It has been found that enteral or parenteral administration of a drug may in certain cases not be adequate to provide a satisfactory effect so that local administration of the drug by means of inserting a device comprising a drug into a specific body cavity into which it will be released and where it will exert its beneficial effect may be an advantage. In this case, too, it would be advantageous to provide drug release by another means than by diffusion from a coating or catheter wall.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a medical device intended for introduction into a body cavity, the device comprising, at one end thereof adapted to be inserted into said body cavity, a matrix in which an active substance is embedded and from which it is released at a predetermined rate, the matrix being composed of a substance which is not or only slightly penetrable to water. The device preferably comprises a tube and/or rod for the drainage and/or delivery of fluids into said body cavity.

The substance composing the matrix must be one which is substantially impenetrable to the body fluids present in the body cavity into which the device of the invention is inserted in order to avoid degradation of the active substance residing in the matrix due to the action of water in case of an active substance which is susceptible to hydrolysis. The inclusion of the active substance in a matrix into which water will not diffuse or only diffuse to a limited extent will thus impart a long-term stability to the drug so that the active substance will in fact remain active even when the device has lodged in the body cavity for quite some time. As body fluids can only act on the surface of a matrix of this type, the active substance embedded therein is only exposed to the body fluids in question when it is

released or immediately prior to its release from the matrix. A matrix of a type which is substantially not penetrable to water will therefore ensure the stability of the active substance in the matrix for the entire period of time when the device is present in the body cavity, until the time when the active substance is released, and will also ensure a constant and reproducible release rate of the active substance from the matrix since the release proceeds gradually from the surface or surfaces of the matrix exposed to the body fluids in question. The release rate of the drug is constant either in the sense that a constant amount of active substance is released at any point during the presence of the device in the body cavity or in the sense that the drug is released in "bursts" (relatively larger amounts at a time) at constant intervals.

In the present context the expression "drainage and/or delivery of fluids" is understood to mean that the device of the invention may be one used either for the removal of waste materials from a body cavity, e.g. a urethral catheter or ostomy appliance, or one which, conversely, is used for the supply of nutrients or medicaments to a person in need thereof, e.g. by infusion through a venous catheter. The body cavity in which the tube and/or rod portion of the device is inserted may for instance be a blood vessel, the stomach, a selected part of the intestines, the middle ear, the urinary bladder, the renal pelvis, the gall bladder, the uterus, the respiratory tract, or an infectious, malignant, traumatic or similar cavity.

The rate at which the active substance is released from the matrix is a predetermined rate, i.e. a rate which is controllable and preferably constant over a certain period of time. The release rate required in each particular instance may *inter alia* depend on the amount of active substance to be released for it to exert the desired effect, as well as on the overall dosage of the active substance contained in the matrix. The substance of which the matrix is composed may therefore be selected according to one or more of these criteria to ensure the desired level of release of the active substance.

In another aspect, the present invention relates to a method of delivering an active substance to a body cavity, the method compris-

ing introducing a medical device of the invention into said body cavity. More specifically, the invention relates to a method of preventing or reducing the incidence of infections arising from the use of medical devices comprising a tube and/or rod one end of which is introduced into a body cavity, the method comprising providing the end of said tube and/or rod inserted into said body cavity with a body formed from a matrix of a hydrophobic substance in which an active substance selected from an antimicrobial, antiviral, antiinflammatory or antiseptic agent is embedded. Local administration of an antibiotic or similar agent at the site where infections may potentially occur has the advantage that lower dosages of the drug will normally be required when the antibiotic is administered systemically.

In a further aspect, the present invention relates to the use of a matrix of a hydrophobic substance in which an active substance is embedded, the active substance being selected from an antimocrobial, antiviral, antiinflammatory or antiseptic agent, for preventing or reducing the incidence of infections arising from the use of medical devices comprising a tube and/or rod, one end of which is inserted into a body cavity, the matrix being provided at said end of the tube and/or rod.

The invention also relates to a method of preventing or treating cancers or neoplasms which comprises introducing a medical device as described above as well as in the following detailed disclosure of the invention into a body cavity, preferably the body cavity where the malignancy is found, the active substance embedded in the matrix being selected from antineoplastic and cytostatic agents.

The invention further relates to the use of a device according to the invention for the treatment or prevention of cancers or neoplasms, the active substance being embedded in the matrix being selected from an antineoplastic and cytostatic agent.

The device of the invention has the further advantage that the dosage of the active substance included in the matrix may be measured so that an appropriate constant dosage thereof will be available at the

site where the active substance exerts its activity for the entire period of time that the device is present in the body cavity; the nature of the matrix substance, i.e. its water-impenetrability, prevents degradation by hydrolysis or other means of the drug due to diffusion of water into the matrix even if the drug in itself is unstable in an aqueous environment. This means that the device of the invention may also be employed to prevent the occurrence of a disease, e.g. an infection, over longer periods of time.

Apart from the advantage arising from the non-diffusibility property of the matrix substance, the device according to the present invention presents the important advantage that it permits substantially direct delivery of an active substance to or close to the site where it will exert its activity. It may therefore be possible to use considerably lower dosages of the active substance in question by such local administration than when the active substance is administered systemically. This may be particularly important in the case of chemotherapeutic agents used as cytostatic or antineoplastic agents many of which have extremely unpleasant side effects at the dosage levels at which they are currently administered. Due to the controlled release of the active substance obtainable from the device of the invention it is also possible to obtain a substantially constant rate of release of the drug over a specific period of time corresponding to the dosage necessary for the treatment in question so that adherence to a strict dosage regimen requiring administration of a drug at set intervals up to several times a day may be dispensed with.

DETAILED DISCLOSURE OF THE INVENTION

In one embodiment of the device of the invention the matrix is one which is gradually eroded in the presence of body fluids whereby the active substance embedded in the matrix is released. Thus, the matrix may be one which is eroded by blood, saliva, peritoneal fluid, cerebrospinal fluid, lymph, interstitial fluid, vaginal or uterine discharge, urine or gastric juice. It is an important requirement that the erosion be of the so-called "heterogenous" type, i.e. the erosion proceeds only from the surface or surfaces of the matrix ex-

posed to the erosive agent, rather than by homogeneous erosion which involves simultaneous degradation of the entire matrix. A heterogenous erosion will result in a constant release, as defined above, of the active substance since the surface area of the matrix may be designed to remain substantially constant. Furthermore, the release rate of the active substance will correspond to the rate of erosion of the matrix, and a desired release rate of a specific active substance may therefore be obtained by selecting the substance composing the matrix according to it erosion properties in a particular erosive agent. Although the desired erosion rate will vary according to the intended use of the device of the invention, and the nature of the active substance included therein and the surface area of the matrix exposed to erosion, the erosion of the matrix should preferably proceed at a slow rate, e.g. a rate of about 0.01-10 mm a day, in a specific body fluid at a temperature of 37°C +/- 2°C.

Apart from this, it is an advantage that the matrix substance itself as well as its degradation products be biocompatible so that it does not give rise to adverse reactions either locally or systemically in the form of allergic or toxic reactions. The matrix material is also preferably compatible with the materials used for medical devices of the present type, e.g. polyvinyl chloride or polyurethane.

The erosion reaction may, for instance, be of the following types: a reaction whereby water-insoluble macromolecules are converted to water-soluble macromolecules by reaction of a side chain, e.g. methyl, or a reaction whereby high molecular weight water-insoluble macromolecules are converted to smaller water-soluble molecules by hydrolytic cleavage of labile bonds in the polymer backbone.

Examples of matrix substances, including erodible substances as defined above, which are useful for the present purpose are a polymer, e.g. polyamide, polyurethane, silicone, polyester, polycarbonate, polyacetal, polycetal, polycaprolactone, a polyalkylene glycol such as polyethylene glycol or polypropylene glycol, a polyalkylene such as polyethylene, a polyalkylene oxide such as polyethylene oxide, poly(ortho)ester, a peptide, polypeptide or protein such as collagen or gelatin, a polysaccharide such as starch or a starch derivative,

cellulose or a cellulose derivative, polylactic acid, polyglycolic acid, or any derivative, mixture or copolymer thereof; a higher alkane such as an alkane with 14 or more carbon atoms; a higher alkene such as an alkene with 18 or more carbon atoms; a fatty acid or fatty acid alcohol or fatty acid ester; or a steroid, e.g. cholesterol and its derivatives, or a combination thereof.

In cases where the matrix substance is an erodible substance, the active substance may be substantially uniformly distributed throughout the matrix. This will ensure a substantially constant or uniform release rate of the active substance which is desirable in some cases. Alternatively, the active substance may be arranged in substantially transverse layers in the matrix. This will lead to the release of the active substance in bursts occurring at set, predetermined intervals. These two release patterns may also be combined so that a uniform release of one active substance (perhaps at a fairly low dosage level) alternates with the release in bursts of the same or another active substance (possibly at a higher dosage level).

In an alternative embodiment of the device of the present invention, the matrix is not necessarily erodible, but the active substance embedded in the matrix is a hydrophilic substance which is at least partly accessible to body fluids when the device is inserted into a body cavity and which dissolves in the presence of said body fluids so as to attract liquid into the solution of said active substance by osmosis, resulting in an increased volume of the solution and thus a localized disruption of the matrix in the vicinity of the active substance, whereby the active substance is released. In cases where the active substance is not in itself a hydrophilic substance, it may be combined with a hydrophilic substance which is at least partly accessible to body fluids when the device is inserted into a body cavity and which dissolves in the presence of said body fluids so as to attract liquid into the solution of said hydrophilic substance by osmosis, resulting in an increased volume of the solution and thus a localized disruption of the matrix in the vicinity of the hydrophilic substance, whereby the active substance with which it is combined is released. In the latter instance, the hydrophilic substance is, in the following, occasionally defined as a hydrophilic auxiliary sub-

stance. In this embodiment, the hydrophilic substance, whether active or auxiliary, may be further defined as water-soluble.

The hydrophilic active substance or, if the active substance is not in itself hydrophilic, the hydrophilic auxiliary substance should be present in an amount which gives rise to a concentration of ions in the solution of the substance which will create a sufficiently high osmotic pressure to attract the required quantity of water resulting in a localized disruption of the matrix. The extent of the localized disruption will *inter alia* be determined by the desired rate of release of the active substance, but should in any case be sufficient to make another part of the hydrophilic substance accessible to body fluids so as to ensure a progressive disruption of the matrix from the surface inwards at a substantially uniform rate. The amount of hydrophilic water-soluble substance to be included in the matrix varies according to the specific substance selected and the way in which it is arranged in the matrix, but the water-soluble substance is generally included in amounts up to 50% by weight of the matrix.

Examples of a substance which dissolves in the presence of body fluids and which fulfil the criteria indicated above with respect to their ability to create an adequate osmotic pressure are a salt, e.g. an alkali metal or alkaline earth metal salt such as sodium chloride, sodium bicarbonate, sodium sulfate, sodium fluoride, potassium chloride, potassium bicarbonate, magnesium chloride, magnesium phosphate, calcium chloride, etc., a sugar such as glucose, fructose, sucrose, lactose etc., an amino acid such as glycine, an alcohol such as propylene glycol, glycerol, etc., urea, or a polymer such as a starch, a peptide or polyethylene glycol, polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol or salts or derivatives thereof, or a mixture thereof.

Rather than being a water-soluble hydrophilic substance, the active substance or the substance with which is combined may be a hydrophilic substance which is at least partly accessible to body fluids and which swells in the presence of said body fluids resulting in a localized disruption of the matrix in the vicinity of the hydrophilic substance whereby the active substance with which the active sub-

stance is combined is released. The considerations indicated above concerning the ability of water-soluble hydrophilic substances to cause localized disruption of the matrix are also applicable to hydrophilic swellable substances. The amount of hydrophilic swellable substance incorporated in the matrix varies according to its swelling power and the way in which it is arranged in the matrix, but the swellable substance is generally included in amounts up to 50% by weight of the matrix in order to ensure the desired result.

The hydrophilic substance may be a hygroscopic substance which swells in the presence of water, and may, for instance be selected from a polymer such as a cellulose derivative, e.g. methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methylpropyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate, cellulose acetate phthalate, gelatin, agar, karaya, guar gum, acacia, pectin, etc.

It should be noted that, in the present context, the term "hydrophilic" is understood to mean a substance which has a strong affinity for water in the sense that it either is soluble in water or swells in the presence of water.

In a currently preferred embodiment of the device of the invention, the active substance or the hydrophilic substance with which it is combined forms particles which are substantially uniformly distributed throughout the matrix. In this case, the matrix may be produced by mixing the active substance or a pre-formed combination of the active substance and the hydrophilic substance with the matrix material so as to obtain a substantially uniform dispersion of the active substance or combination of active substance with hydrophilic substance therein. The optional combination of the active substance with the hydrophilic substance may be in the form of either a mixture of particles of either substance, or particles of the active substance may be coated with the hydrophilic substance. In this embodiment, the limited progressive disruption of the matrix gives rise to the formation of a honeycombed or sponge-like structure in the matrix.

In another embodiment of the device of the invention, the active substance or the hydrophilic substance with which the active substance is combined forms one or more rod-like bodies extending substantially longitudinally through the matrix. In this case, the hydrophilic substance will preferably be one which swells in the presence of body fluids since, if it is a water-soluble substance, it and the active substance combined with it, will simply be flushed fairly quickly from the matrix so that no adequate sustained release effect will be obtained. A swellable substance, on the other hand, will gradually take up water followed by swelling and disruption of the matrix in the vicinity of the swollen portion of the hydrophilic substance and consequently a gradual release of the active substance. In this embodiment, the active substance may be combined with the hydrophilic substance by mixing the active substance with the hydrophilic substance.

In a further embodiment of the device of the present invention, the active substance or the hydrophilic substance with which the active substance is combined forms one or more layers extending substantially longitudinally or transversely through the matrix, alternating with layers of the matrix. If the layers are longitudinally extending, the hydrophilic substance should preferably be a swellable substance for the reasons stated above. If the layers are transversely extending, the hydrophilic substance may be either water-soluble or swellable, use of a water-soluble substance, however, tending to lead to an immediate release in bursts of the active substance.

The matrix may be produced by placing alternating layers of the matrix material and the active substance, optionally combined with a hydrophilic substance, on top of each other in a sandwich-like structure. For example sheets of such alternating layers may be prepared and matrix bodies of the desired size and shape may be punched from the sheets. When the layers are tranversely extending, the thickness of the matrix layers alternating with the layers comprising the active substance should be so calculated that the matrix will be disrupted, due to the increased volume of the solution of the soluble substance caused by osmosis or due to swelling of the hydrophilic substance, to such an extent that at least part of the next layer of

the hydrophilic active or auxiliary substance will be exposed to body fluids.

When the layers are longitudinally extending, the thickness of the matrix and hydrophilic layers may be so designed that the matrix will disrupt substantially immediately on contact with body fluids so that all of the active substance will be released at once. This may be advantageous in case of, for instance, an already established and progressing infection where a large initial dosage of an antibiotic is needed to combat it. Such a type of matrix may be combined with a slow-release matrix, e.g. one of the other embodiments described above so that the tube and/or rod end of the device of the invention will contain two types of matrices, one intended for immediate effect and the other intended for long-term action of the active substance.

It should be noted that when the matrix comprises an active substance optionally combined with a hydrophilic substance the matrix may further comprise the same or another active substance which is not in itself hydrophilic or combined with a hydrophilic substance. This active substance may be embedded in the matrix material and released as a result of the limited disruption of the matrix.

When the active substance is not in itself a hydrophilic substance, the hydrophilic substance with which it is combined need not necessarily be a therapeutically inert auxiliary substance but may advantageously be another active substance. Thus, a matrix of the types described above may be used to prepare combination formulations of active substances which are released gradually and substantially simultaneously to exert different therapeutic effects or possibly a synergistic effect.

The active substance or substances included in the device of the invention may be selected from many therapeutic categories, in particular from substances which may advantageously be administered locally in or through a body cavity. Examples of such substances are antimicrobial agents, anesthetics, analgesics, antiinflammatory agents, antiseptic agents, growth factors, hormones, disinfectants, counterirritants, coagulation modifying agents, wound-healing

promoters, antiviral agents and antineoplastic or cytostatic agents or other agents with anticancer properties, or a combination thereof.

Suitable antimicrobial agents may be selected from aminoglycosides e.g. gentamycin, quinolones, chloramphenicols, teteracyclins, penicillins, cephalosporins, monobactams, fosidic acid, sulfonamides, sulfones, neomycin, polymyxin B, bacitracin and combinations thereof, the combination of neomycin and polymyxin B being particularly preferred. Additional suitable antimicrobial agents include nitrofurantoin, hexamine and derivatives thereof, nalidixic acid, oxolinic acid and other quinoline derivatives, trimethoprim, cephamycins, lincomycins, macrolides, rifamycins, spectinomycin and vancomycin. Any of the above antimicrobial agents may further be used in combination with penicillinase inhibitors. Suitable antifungal agents include griseofulvin, candidicin, amphotericin, natamycin, nystatin, imidazole derivatives and fatty acid antifungals. Suitable antiparasitic agents include metronidazole and other antiprotozoal agents. Suitable antiviral agents include idoxuridine, cytarubine, amantadine, acyclovir, interferons, ribavirin and vidarabine. Suitable antiinflammatory agents include steroids and NSAID agents. Suitable antiseptic agents may be selected from mandelic acid and derivatives thereof, hippuric acid, dyes and formaldehyde. Suitable antineoplastic and cytostatic agents include, but are not limited to, doxorubicin (adriamycin), methotrexate, BCG vaccine, fluorouracil and thio-TEPA. Suitable counterirritants may be selected from antihistamines, camphor and bismuth salts. Suitable wound-healing promoters include, but are not limited to, collagen, hyaluronic acid, polysulfated saccharides such as sucralfate, zinc salts and vitamin A.

In order to obtain an improved control of the release of an active substance from the matrix, in particular with respect to defining a particular surface with a known surface area from which the release of the active substance takes place, the matrix may be provided with a coating which has an opening of a defined size and geometry through which opening the active substance is released. The coating is one which is substantially impermeable and resistant to the body fluid with which the device is contacted so as to substantially prevent

release of the active substance through the coating. Such a coating may be selected from polyurethane, polyethylene, silicone, latex, polyvinylchloride, polyhydroxybutyrate, polyhydroxyvalerate, or a mixture thereof. The coating may be applied by spraying a coating material onto the matrix in such a way that an opening is left in the coating (this may, for instance, be done by spraying a rod formed from the matrix with a coating solution or suspension and subsequently cut it into smaller segments, the end portions of which are not coated). The coating may also be applied by dipping a pre-formed body of the matrix into a coating solution or suspension, taking care that not all of the body is immersed, or by coextrusion.

In the device of the invention, the matrix is preferably formed into a body of a suitable shape and size adapted to the intended end use of the device. Thus, the body formed from the matrix may be attached to or form the tip of the tube and/or rod. In this embodiment, the matrix may be formed into a rod of a suitable diameter (determined by the type of device to which the matrix will be attached) which is divided into smaller segments of an appropriate length, optionally after applying a coating as described above. These segments may then be glued to the tip of the tube and/or rod by means of a non-toxic, pharmaceutically acceptable glue in a manner known *per se* from the prepartion of conventional catheters. Before or after attachment of the matrix body, the tip end thereof is preferably rounded so as to avoid discomfort and/or damage when the tube and/or rod is inserted into the body cavity in question. The matrix may also be formed into a conventional suppository body of an appropriate size, for instance by moulding in a manner known *per se*. Such matrix bodies may then be attached to the tip of the tube and/or rod as indicated above, optionally after applying a coating as described above.

Alternatively, the matrix may be extruded into a pre-formed tube of an appropriate diameter, and the tube is subsequently cut into smaller segments of an appropriate size so as to leave well-defined openings at the ends of the segments. The segments may then be attached to the tip of the device as explained above leaving an opening at the tip end of the segment where the matrix is accessible to body fluids. In this case, too, the tip end of the segment is preferably

rounded so as to avoid possible injury or discomfort arising from the insertion of the tube. It should be noted that, in the present context, the wall portion of the tube segment comprising the matrix is also considered to constitute a coating.

In another embodiment, the body formed from the matrix is located inside the tube and/or rod part of the device. This may for instance be done by extruding the matrix into the tube at an appropriate site. The matrix body will often be placed into a tip portion of the tube (in particular if the tube forms part of a catheter), but the matrix may, however, also be placed at a different site of the tube, the exact location of the matrix body being determined by the nature of the device of which it forms a part. In this case, no coating need be applied on the matrix as the surface area from which release of the active substance takes place is delimited by the wall(s) of the tube portion of the device itself.

The device of the invention may be any device of the type which is provided with a tube and/or rod to be inserted into a body cavity. In particular, the device may be selected from a catheter, such as an arterial, venous or urethral catheter, probe, drainage tube, e.g. a middle ear drainage tube, endoscopic device, respiratory aid device and ostomy device.

DESCRIPTION OF THE DRAWING

The invention is further described with reference to the drawings in which

Fig. 1 is a partly sectional side view of a currently preferred embodiment of a device of the present invention, and

Fig 2. is an enlarged sectional view of a tip of the device shown in Fig. 1.

In Fig. 1, a urethral catheter 10 is shown comprising a tube portion 12 and a tip portion 14 attached thereto. The tube portion 12 is provided with a thin-walled outer sheath of a flexible plastic material

which sheath is adapted to provide a balloon 16 by inflation adjacent to the tip of the catheter 10. The catheter is further provided with a drainage inlet 18, a drainage outlet 20, and an inlet end 22 for the introduction of liquid for the inflation of the balloon 16 so as to retain the tip portion 14 in the bladder.

In Fig. 2, the tip portion 14 is shown comprising a matrix body 30 provided with a coating 26 and comprising particles 28 of an active substance.

The invention is further disclosed in the following non-limiting examples.

EXAMPLE 1

30 g of sodium chloride crystals were mixed thoroughly with 5 g of Patent Blue. The resulting particles were mixed with a silicone monomer to obtain a uniform distribution of the particles in the matrix. The monomer was then subjected to cold-curing (room temperature vulcanization) in a manner known *per se*. The final matrix contained 60% of silicone, 30% of sodium chloride and 10% of Patent Blue.

Before the polymerization reaction of the silicone monomers was complete (i.e. during vulcanization), the matrix was extruded into a pre-formed silicone tube with an internal diameter of 4 mm by means of a syringe. The tube was then cut into segments with a length of about 2 cm which were glued to the tip of an Arguille catheter No. 12 (composed of latex coated with silicone) in a manner known *per se* for attaching tips to catheters. The tip end of the tube segment was rounded by shaving it with a scalpel.

EXAMPLE 2

Patent Blue was mixed thoroughly with a molten polyethylene glycol (PEG) 20000-matrix material. The final matrix contained 25% of Patent Blue and 75% of PEG 20000. While hot, the matrix was extruded into a

pre-formed silicone tube with an internal diameter of 4 mm by means of a syringe and left to cool. The tube was then cut into segments with a length of about 2 cm. The tube segments were then glued to the tip of a catheter as described in Example 1.

EXAMPLE 3

By proceeding in a similar way as described in Example 2, but using a matrix material composed of 90% PEG 20000 and 10% PEG monostearate, tube segments were prepared containing 75% of the matrix material and 25% of Patent Blue. The tube segments were then glued to the tip of a catheter as described in Example 1.

EXAMPLE 4

By proceeding in a similar way as described in Example 2, but using PEG 20000 as the matrix material and neomycin as the active substance, tube segments were prepared containing 75% PEG 20000, 10% of neomycin and 15% of Patent Blue. The tube segments were then glued to the tip of a catheter as described in Example 1.

EXAMPLE 5

The catheter produced in Example 2 was inserted into the bladder of a female pig through the urether. The amount of pigment (Patent Blue) released from the matrix was measured spectrophotometrically and was found to be constant over a period of three days.

CLAIMS

1. A medical device intended for introduction into a body cavity, the device comprising, at one end thereof adapted to be inserted into said body cavity, a matrix in which an active substance is embedded and from which it is released at a predetermined rate, the matrix being composed of a substance which is not or only slightly water-penetrable.

2. A device according to claim 1, comprising a tube and/or rod for the drainage and/or delivery of fluids into said body cavity.

3. A device according to claim 1 or 2, wherein the matrix is one which is gradually eroded in the presence of body fluids whereby the active substance embedded in the matrix is released.

4. A device according to claim 1 or 2, wherein the matrix is composed of a polymer, e.g. polyamide, polyurethane, silicone, polyester, polycarbonate, polyacetal, polycetal, polycaprolactone, a polyalkylene glycol such as polyethylene glycol or polypropylene glycol, a polyalkylene such as polyethylene, a polyalkylene oxide such as polyethylene oxide, poly(ortho)ester, a peptide, polypeptide or protein such as collagen or gelatin, a polysaccharide such as starch or a starch derivative, cellulose or a cellulose derivative, polylactic acid, polyglycolic acid, or any derivative, mixture or copolymer thereof; a higher alkane such as an alkane with 14 or more carbon atoms; a higher alkene such as an alkene with 18 or more carbon atoms; a fatty acid or fatty acid alcohol or fatty acid ester; or a steroid, e.g. cholesterol and its derivatives, or a combination thereof.

5. A device according to claim 3 or 4, wherein the active substance is substantially uniformly distributed throughout the matrix.

6. A device according to claim 3 or 4, wherein the active substance is arranged in substantially transverse layers in the matrix.

7. A device according to claim 1 or 2, wherein the the active substance embedded in the matrix is a hydrophilic substance which is at least partly accessible to body fluids when the device is inserted into a body cavity and which dissolves in the presence of said body fluids, so as to attract liquid into the solution of said active substance by osmosis, resulting in an increased volume of the solution and thus a localized disruption of the matrix in the vicinity of the active substance, whereby the active substance is released.

8. A device according to claim 1 or 2, wherein the active substance embedded in the matrix is combined with a hydrophilic substance which is at least partly accessible to body fluids when the device is inserted into a body cavity and which dissolves in the presence of said body fluids so as to attract liquid into the solution of said hydrophilic substance by osmosis, resulting in an increased volume of the solution and thus a localized disruption of the matrix in the vicinity of the hydrophilic substance, whereby the active substance with which it is combined is released.

9. A device according to claim 7 or 8, wherein the substance which dissolves in the presence of body fluids is a salt, e.g. an alkali metal or alkaline earth metal salt such as sodium chloride, sodium bicarbonate, sodium sulfate, sodium fluoride, potassium chloride, potassium bicarbonate, magnesium chloride, magnesium phosphate, calcium chloride, etc., a sugar such as glucose, fructose, sucrose, lactose etc., an amino acid such as glycine, an alcohol such as propylene glycol, glycerol, etc., urea, or a polymer such as a starch, a peptide or polyethylene glycol, polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol or salts or derivatives thereof, or a mixture thereof.

10. A device according to claim 1 or 2, wherein the active substance embedded in the matrix is a hydrophilic substance which is at least partly accessible to body fluids and which swells in the presence of said body fluids resulting in a localized disruption of the matrix in the vicinity of the hydrophilic substance whereby the active substance is released.

11. A device according to claim 1 or 2, wherein the active substance embedded in the matrix is combined with a hydrophilic substance which is at least partly accessible to body fluids and which swells in the presence of said body fluids resulting in a localized disruption of the matrix in the vicinity of the hydrophilic substance whereby the active substance with which the active substance is combined is released.

12. A device according to claim 10 or 11, wherein the hydrophilic substance is a hygroscopic substance which swells in the presence of water.

13. A device according to claim 12, wherein the hygroscopic substance is a polymer such as a cellulose derivative, e.g. methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methylpropyl cellulose, hydroxypropylmethyl cellulose, cellulose acetate, cellulose acetate phthalate, gelatin, agar, karaya, guar gum, gum arabic, pectin, etc.

14. A device according to any of claims 7-10, wherein the active substance or the hydrophilic substance with which the active substance is combined forms particles which are substantially uniformly distributed throughout the matrix.

15. A device according to any of claims 7-10, wherein the active substance or the hydrophilic substance with which the active substance is combined forms one or more rod-like bodies extending substantially longitudinally through the matrix.

16. A device according to any of claims 7-10, wherein the active substance or the hydrophilic substance with which the active substance is combined forms one or more layers extending substantially longitudinally or transversely through the matrix, alternating with layers of the matrix.

17. A device according to claim 12, wherein the hydrophilic substance is another active substance.

18. A device according to any of the preceding claims, wherein the active substance is selected from antimicrobial agents, anesthetics, analgesics, antiinflammatory agents, antiseptic agents, hormones, disinfectants, counterirritants, coagulation modifying agents, wound-healing promoters, antiviral agents and antineoplastic or cytostatic agents or other agents with anticancer properties, or a combination thereof.

19. A device according to claim 1 or 2, wherein the matrix is provided with a coating which has an opening of a defined size and geometry through which opening the active substance is released, the coating being one which is substantially impermeable and resistant to the body fluid with which the device is contacted.

20. A device according to claim 19, wherein the coating is selected from polyurethane, polyethylene, silicone, latex, polyvinylchloride, polyhydroxybutyrate, polyhydroxyvalerate, or a mixture thereof.

21. A device according to any of the preceding claims, wherein a body formed from the matrix is attached to or forms the tip of said tube and/or rod.

22. A device according to any of claims 1-20, wherein a body formed from the matrix is located inside said tube and/or rod.

23. A device according to any of the preceding claims, which is selected from a catheter, such as an arterial, venous or urethral catheter, probe, drainage tube, e.g. a middle ear drainage tube, endoscopic device, respiratory aid device and ostomy device.

24. A method of delivering an active substance to a body cavity, comprising introducing into a body cavity a medical device according to any of claims 1-23.

25. A method of preventing or reducing the incidence of infections arising from the use of medical devices comprising a tube and/or rod one end of which is introduced into a body cavity, the method

comprising providing the end of said tube and/or rod inserted into said body cavity with a body formed from a matrix of a hydrophobic substance in which an active substance selected from an antimicrobial, antiviral or antiseptic agent is embedded.

26. Use of a matrix of a hydrophobic substance in which an active substance is embedded, the active substance being selected from an antimicrobial, antiviral or antiseptic agent, for preventing or reducing the incidence of infections arising from the use of medical devices comprising a tube and/or rod, one end of which is inserted into a body cavity, the matrix being provided at said end of the tube and/or rod.

27. A method of preventing or treating cancers or neoplasms, the method comprising introducing a medical device according to any of claims 1-23 into a body cavity, the active substance being selected from antineoplastic or cytostatic agents or other agents with anticancer properties.

28. Use of a medical device according to any of claims 1-23 in which the active substance is selected from an antineoplastic and cytostatic agent for the treatment or prevention of cancer or neoplasms.

Fig. 1

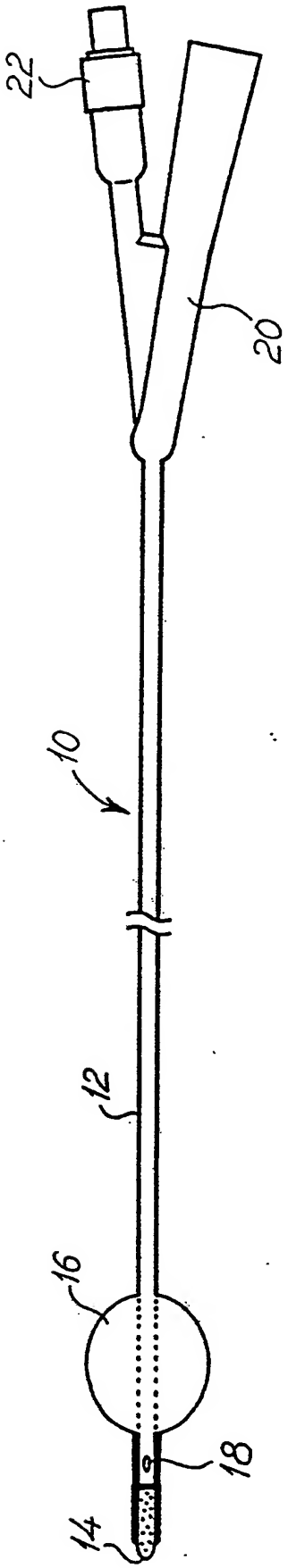
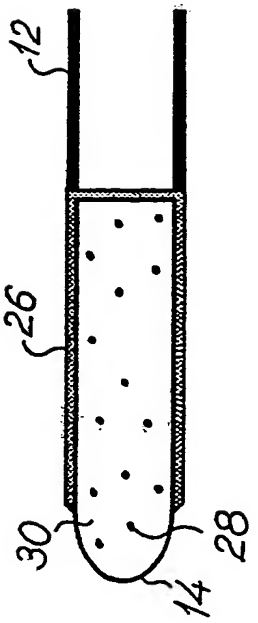


Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No PCT/DK88/00163

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC4

A 61 M 31/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	A 61 M 23/00, 25/00, 27/00, 31/00, 37/00, 37/04
US Cl	128:260, 264, 267, 348-350; 604:48, 49, 57, 64, 265, 285, 288

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	DE, A1, 3 419 876 (HARMAN, S.MITCHELL) 28 November 1985	1, 3
A		4-20
X	US, A, 2 882 900 (J.W. HOLTER) 21 April 1959	1, 3
X	US, A, 3 297 031 (H.F. BRAY) 10 January 1967	1, 3
A	US, A, 1 888 349 (C.M. JACOBY) 22 November 1932	1, 2, 23
A	US, A, 4 603 152 (LAURIN ET AL) 29 July 1986	1, 2, 23
A	US, A, 3 924 622(BROOKE) 9 December 1975 See especially column 5,lines 55-57	4-20
A	US,A, 3 926 188 (BAKER ET AL) 16 December 1975	4-20
A	US, A, 4 351 337(SIDMAN) 28 September 1982	4-20

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-12-23	1989 -03- 09
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Leif Vingård

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 24,25,27 because they relate to subject matter not required to be searched by this Authority, namely:

methods for treatment of the human or animal body by therapy(Rule 39.1 (iv))

2. [ ] Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.